REMARKS

As a preliminary matter, it is noted that the cover sheet for the Office Action refers, under items 4 and 6, and under paragraph 5 on page 4, to claims "208-214". It is assumed that this was a typographical error for claims "208-212", since there were no claims numbered 213 and 214 in the application.

Claims 151, 153-163, 166, 167, 170, 177, 180, 181, 183, 184, 186, 188, 190, 209, and 211 have been canceled. Applicants emphasize that such cancellation is made without waiver or prejudice to Applicants' right to file one or more Continuation applications directed to such canceled subject matter. The cancellation is made to narrow the issues in that the claims are now directed to controlled release dosage forms that operate predominantly by a delayed release mechanism, i.e., by releasing the bulk of their contained azithromycin in a portion of the gastrointestinal tract distal to (i.e., that portion of the GI tract occurring after or below) the duodenum.

Claims 149, 150, 152, 164, 165, 168, 169, 171-176, 178, 179, 182, 185, 187, 189, 208, 210, and 212 remain in the application.

Claims 149, 171, and 172 have been formally amended simply to improve the claim wording and correct typographical errors (e.g., in claim 149, among other wording changes, the phrase "dosage form" replaces the word "rate" as the correction of an obvious typographical error).

Claim 178 has been currently amended to eliminate dependence from a canceled claim.

New claims 213, 214, 215, 216, 217 and 218 have been added. These parallel canceled claims 154-157 and 162-163, respectively, and are supported thereby. No additional fees are due for these new dependent claims since at least an equal number of dependent claims has been canceled.

All claims currently in the application stand rejected under 35 USC §103(a) as being unpatentable over Curatolo (US 5,605,889) in view of Morashita et al (Drug Design and Delivery, 1991). The Examiner stated, in pertinent part:

> Curatolo et al. teaches a dosage form of azithromycin which can be administered to a mammal. The azithromycin can be in various forms such as a pharmaceutically acceptable salt, anhydrous or hydrous, or as a dihyrate and are formulated from about 25 mg to about 3 grams (col. 4, lines 51-61). Column 2, lines 45-54 teach that the composition can be administered as a tablet or in unit dosage packets "sachet" comprising the azithromycin and a pharmaceutically

acceptable carrier. Column 6, lines 62-67 teach the use of binders such as cellulose derivatives. It is taught in column 8, lines 19-27 that the drug could be formulated into a powder for the purposes of making oral suspensions. Column 7, lines 61-64 teach that a coating can be employed. The prior art does not teach the dosage form being delivered to the gastrointestinal tract as claimed. It is also not taught the dosage form comprising a plurality of microparticles.

Morishita et al. teaches controlled-release preparations such as enteric-coated and sustained release preparations which are designed to enable a drug release at a limited segment or through the whole region of the gastrointestinal tract (introduction). The preferred enteric-coated is Eudragit L100, a pH-dependent copolymer.

It is the object of the present application to release the drug in a portion of the gastrointestinal tract distal to the duodenum to avoid gastrointestinal side effects. It would therefore be obvious to one of ordinary skill in the art to use the coatings of Morishita which teaches that the coatings are designed to release the preferred amount of drug at a limited segment or through the whole region of the gastrointestinal tract with the preparations of Curatolo. The expected result would be an oral dosage form that releases a specific amount of drug in a specific region i.e. distal to the duodenum and that would aid to avoid gastrointestinal side effects. It would also have been obvious to one of ordinary skill in the art to formulate the dosage form containing a plurality of particles for the purposes of controlling the drug release rate. (Office Action, pages 3-4)

The Office Action is traversed on the basis that (1) the references are not properly combinable and (2) the rejection is based on hindsight. It is Applicants' position that Curatolo, which is directed to quick release, in fact teaches away from Morashita, which is directed to controlled release (not to mention that it is also directed to erythromycin, a different drug). One of ordinary skill in the art would simply not find it obvious to combine a reference directed to fast release (Curatolo), with a reference that in essence seeks to do the opposite, i.e., delay the release of a drug. More specifically, and contrary to the Examiner's assertion, one of ordinary skill would not find it obvious to put an enteric coating (Morashita) on a dosage form expressly designed for fast and/or immediate release (Curatolo). That is, an enteric coating as taught by Morishita applied to a dosage form as taught by Curatolo would delay the release of azithromycin, thereby defeating the purpose (immediate/fast release) stated in Curatolo. It is well settled law that if references are to be combined, there (1) must be a suggestion to combine them grounded in the prior art and (2) the prior art must provide an expectation of success.

> Mere fact that teachings found in prior art could be combined as proposed by patent examiner does not make combination obvious absent some teaching, suggestion, or incentive supporting proposed combination; in present case,

> examiner failed to identify any such teaching, suggestion, or incentive to support proposed combination of two prior art references (Ex parte Metcalf, BdPatApp&Int (unpub), 5/2/03) . . . Page 1633

Also, see In re Bond, 15 Uspq2d 1566 (Fed. Cir. 1990) in which it was held that the PTO erred in rejecting a claimed invention as an obvious combination of the teachings of two prior art references when the prior art provided no teaching, suggestion, or incentive supporting the combination. See also Smithkline Diagnostics v. Helena Laboratories Corp., 8 USPQ2d 1468, where the court stated that a challenger to the validity of a patent "cannot pick and choose among the individual teachings of assorted prior art references to recreate the claimed invention"; the challenger has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination. See also In re Mahurkar Patent Litigation, 28 USPQ2d 1801 (N.D. Ill. 1993) where it was stated that decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming it is easy to reassemble these elements into the invention is a forbidden *ex post* analysis.

Applying the law to the instant rejection, there is clearly no basis for combining Curatolo and Morashita, particularly in view of the fact that each document teaches away from the other.

Curatolo is not addressed to and does not disclose controlled release dosage forms. Curatolo in fact teaches immediate and/or fast release and, accordingly, teaches away from the instant invention. Curatolo is grounded in the determination that certain dosage forms which release azithromycin quickly for dissolution avoid adverse food effects. Quick release and dissolution are therefore important features for the dosage forms disclosed in Curatolo. See, for example, the following quotation from Curatolo:

> The inventors have demonstrated that azithromycin breaks down if exposed to stomach juices which inherently exhibit acid pH. Thus,....it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention. [Curatolo, column 4, lines 30-35]

See also the following quotation:

> It is believed that the azithromycin dosage forms of the invention do not exhibit a food effect in large part because they either provide azithromycin ready for dissolution in the GI tract essentially immediately following ingestion (suspensions) or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution.

Clearly, a touchstone of Curatolo is fast disintegration and/or fast dissolution to provide azithromycin in the GI tract as soon as possible. There are no embodiments disclosed in Curatolo in which a dosage form is deliberately engineered in order to slow down azithromycin release, as in the instant invention, so that the bulk of azithromycin release occurs distal to the duodenum. Applicants' delayed release dosage forms are engineered to release the bulk of their contained azithromycin **after** the duodenum. But, slow (sustained and/or delayed) release is simply not a factor that makes any sense in the context of the primary reference, i.e., in Curatolo's no- or low- food effect dosage forms. Rather, quick and/or immediate release is an important factor in Curatolo, i.e., clearly the opposite of what the inventors are seeking to achieve in the instant invention. The instant invention is, quite simply, focused on a different problem that employs different teachings than Curatolo. Thus one skilled in the art who was interested in achieving azithromycin controlled release, i.e., delayed release as in the instant invention, would dismiss the Curatolo reference out of hand as irrelevant. Most importantly, one of ordinary skill in the art would find no reason supporting combining Curatolo and Morishita since their teachings - - fast release vs. delayed release - - are antithetical to each other.

To summarize, a rejection over the cited references is not tenable because their teachings are opposed. It is not tenable to combine references that teach away from each other. It is not tenable to base a rejection of an azithromycin delayed release dosage form on references that, in part, include teachings of immediate/ fast release as in Curatolo.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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James T. Jones
Attorney for Applicant
Reg. No. 30,561

Pfizer Inc
Patent Department
Eastern Point Road
Groton, CT 06340
(860) 441-4903